REMARKS

Claims 2, 3, 6-9, 12-15, 17-34, and 36 are pending and at issue. With entry of this amendment, claim 2 has been amended and claim 50 has been added. Support for the amendment to claim 2 can be found from page 5, line 26 to page 6, line 3, in Example 8 starting on page 30, line 20, and in Example 11 starting on page 34, line 9 of the application as filed. The structure of "Metabolite A," described in Example 11 as producing cardiovascular side effects, is provided on page 31 in Example 8 and has the chemical name "3-hydroxy anagrelide." Thus, "3-hydroxy anagrelide" can be substituted for the phrase "metabolites exhibiting cardiovascular and/or inotropic side effects" disclosed on page 5, lines 30-31. Support for new claim 50 can be found on page 2, lines 25-31 and page 35, lines 15-20. No new matter has been added to this application. Thus, after entry of this amendment, claims 2, 3, 6-9, 12-15, 17-34, 36, and 50 are pending and at issue.

The amendment to claim 2 and new claim 50 recite the unexpected discovery of the presently claimed invention: transdermally administering anagrelide to minimize first pass live metabolism would reduce the amount of 3-hydroxy anagrelide formed thereby circumventing the adverse side-effects observed when anagrelide is administered orally. This surprising result was discussed on pages 18-19 of the amendment filed on September 19, 2007 and in ¶¶7-8 of the Declaration of Dr. Richard Franklin also filed on September 19, 2007.

Applicant respectfully points out that claims 2, 3, 6-9, 12-15, 17-34, and 36 are pending instead of claims 2, 6-9, 17-26, 28, 30, 32, and 36 as listed on pages 1 and 2 of the Office Action. Moreover, it appears that claims 13-15, 29, 31, 33, and 34 are allowable because these claims have not been rejected in the present Office Action and that (1) the objection to the drawings, (2) the 35 U.S.C. §112, first paragraph, lack of enablement rejection and (2) the 35 U.S.C. §102(b) anticipation rejection from the previous Office Action mailed April 19, 2007 have been withdrawn since they do not appear in the present Office Action. Applicant respectfully requests clarification of the record.

Information Disclosure Statements Attached to the Office Action mailed January 28, 2008

The PTO/SB/08A/B forms (submitted by Applicant on March 19, 2007 and September 19, 2007) mailed with the present Office Action have not been signed by the Examiner. Applicant respectfully requests that the Examiner considers the references on these forms and signs these forms. Applicant also notes that an IDS was submitted on April 20, 2007, but it does not appear that references cited in the April 20, 2007 IDS have been considered. Applicant respectfully requests that these references also be considered.

First Rejection under 35 U.S.C. §103 – Obviousness

Claims 2, 3, 6-9, 12, 17-20, 26, 27, 32, and 36 remain rejected as obvious over U.S. Patent No. 6,194,420 ("Lang") in view of U.S. Patent No. 6,221,383 ("Miranda") and in further view of D'Angelo. The Examiner asserts that Lang teaches anagrelide containing pharmaceutical compositions to treat essential thrombocythemia. According to the Examiner, Miranda describes the transdermal administration of anagrelide. The Examiner asserts that D'Angelo teaches the transdermal delivery of drugs using a patch system. The Examiner contends that one of ordinary skill in the art would be motivated to combine the teachings of Lang with the teachings of Miranda because both describe the administration of anagrelide as part of a pharmaceutical composition. The Examiner further asserts that one skilled in the art would combine the teachings of Lang, Miranda, and D'Angelo because when the teachings of Lang and Miranda are combined, these teachings overlap with D'Angelo in subject matter, *i.e.*, the administration of medicaments, particularly anagrelide, by transdermal delivery.

Second Rejection under 35 U.S.C. §103 – Obviousness

Claims 21-23, 28, and 30 remain rejected as obvious over Lang in view of D'Angelo and in further view of U.S. Patent No. 5,133,972 (" Ferrini"). The Examiner incorporates by reference the discussion of Lang and D'Angelo from the above rejections. Ferrini, according to the Examiner,

teaches a multilayered therapeutic system for the transdermal administration of an active ingredient. The Examiner asserts that a skilled artisan would be motivated to combine Lang, D'Angelo, and Ferrini because each describes the administration of medicaments by transdermal delivery.

Third Rejection under 35 U.S.C. §103 – Obviousness

Claims 24, 25, and 36 remain rejected as obvious over Lang in view of D'Angelo and in further view of U.S. Patent No. 4,847,276 ("Yarrington"). The Examiner incorporates by reference the discussion of Lang and D'Angelo from the above rejections. The Examiner asserts that Yarrington teaches the treatment of thrombocythemia by the administration of anagrelide using particular regimens. According to the Examiner, one of ordinary skill in the art would be motivated to combine the teachings of Lang, D'Angelo, and Yarrington because each relate to the treatment of thrombocythemia.

Applicant's Response to the Obviousness Rejections

Applicant respectfully traverses each of the obviousness rejections.

The present claims would not have been obvious to one of ordinary skill in the art because, as discussed in the response filed September 19, 2007, Applicant unexpectedly discovered that transdermally administering anagrelide to minimize first pass liver metabolism as set forth in the claims would circumvent the formation of 3-hydroxy anagrelide and the adverse cardiovascular side-effects observed when anagrelide is administered orally. This surprising result is discussed in the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Richard Franklin ("the Franklin Declaration"), the present inventor, submitted on September 19, 2007.

To emphasize this unexpected discovery in the claims, Applicant (1) has amended claim 1 to recite that minimizing first pass liver metabolism reduces the plasma concentration of 3-hydroxy anagrelide compared to a patient orally administered the equivalent amount of anagrelide and (2) has presented new claim 50 setting forth that the reduction in the plasma concentration of

the 3-hydroxy anagrelide results in a reduction of the cardiovascular side effects in the patient compared to the cardiovascular side effects of a patient orally administered the equivalent amount of anagrelide.

The Examiner asserts on page 3 of the Office Action that based on Dr. Franklin's Declaration, "[t]he effect appears to be additive rather than synergistic." Applicant points out to the Examiner that the unexpected results discussed in the Franklin Declaration are not related to synergism.

In the Franklin Declaration, summarized in the amendment dated September 19, 2007, Franklin explains his surprising discovery that the adverse cardiovascular side-effects, plaguing many thrombocythemia patients orally treated with anagrelide, were caused by the 3-hydroxy metabolite of anagrelide formed during its first pass liver metabolism (¶ 7 of the Franklin Declaration). *See also* the Citizen Petition dated August 13, 2004 related to anagrelide (*e.g.*, the 3rd complete paragraph on page 8 stating that 3-hydroxy anagrelide is the likely cause of the cardiovascular side-effects observed after the administration of anagrelide and the 4th paragraph on page 11 summarizing that 3-hydroxy anagrelide is formed by first pass liver metabolism, Exhibit 1); the section entitled "Pharmacological Properties" on page 113 of Wagstaff and Keating, *Drugs* 2006, 66:111-131 (the 3-hydroxy anagrelide metabolite is 40 times more potent than anagrelide as an inhibitor of PDEIII resulting in inotropic effects and systemic exposure to 3-hydroxy anagrelide is about twice of the parent in patients with thrombocythemia, Exhibit 2); the abstract of Wang *et al.*, *British Journal of Pharmacology* 2005, 146:324-332 (3-hydroxy anagrelide (*i.e.*, BCH24426) is 40 times more potent than anagrelide as an inhibitor of PDEIII, Exhibit 3).

In his Declaration, Franklin further details that the transdermal administration of anagrelide to minimize first pass liver metabolism and reduce the negative side-effects of orally administered anagrelide was surprising because (1) the 3-hydroxy anagrelide metabolite demonstrates an unprecedented increase in phosphodiesterase III (PDEIII) inhibitory activity in light of its minor structural change compared to the anagrelide parent and (2) adverse side-effects

caused by the metabolite were the very opposite of the detoxification effect expected after liver metabolism of a drug (¶ 8 of the Franklin Declaration). In light of these surprising discoveries, methods of treating thrombocythemia by transdermally administering anagrelide to minimize first pass liver metabolism and to reduce 3-hydroxy anagrelide plasma concentrations and associated cardiovascular side effects compared to orally administered patients as recited in the amended claims would not have been obvious to one of ordinary skill in the art. Thus, Applicant respectfully requests entry of the amendments and withdrawal of each of the obviousness rejections.

Furthermore, for the reasons provided below, the cited references taken separately or in combination do not describe or suggest the treatment of thrombocythemia in patients afflicted by that disease by transdermally administering an effective amount of a skin permeable form of anagrelide to minimize first pass liver metabolism, 3-hydroxy anagrelide formation, and the associated cardiovascular side-effects as recited in the amended claims.

In the previous response dated September 19, 2007, Applicant asserted that Lang primarily discloses the use of the anagrelide metabolite, 2-amino-5,6-dichloro-3,4-dihydroquinazoline, to treat thrombocythemia. This metabolite was subsequently shown to be entirely without activity in reducing blood platelets. Lang also briefly describes routes of administration, including capsule, tablet, enteric coated tablet, IV formulation, nasal spray, and intraperitoneal injection, of the metabolite. The Examiner asserts that Applicant's arguments were contradictory and deduces that, based on Applicant's disclosure, anagrelide can be used to treat thrombocythemia. Applicant agrees that anagrelide can treat thrombocythemia, however as stated in the previous response, Lang does not disclose or suggest any routes of administration for anagrelide.

The Examiner discusses Miranda and D'Angelo on page 3 of the Office Action as follows:

> [a]pplicants also argue that the Miranda patent does not disclose anagrelide as a treatment of thrombosis but rather, only lists anagrelide once as one of over a

> dozen antithromb[ot]ic drugs and that D'Angelo does not describe or suggest the treatment or prevention of thrombocythemia. Admittedly, D'Angelo is a broad patent, and it does list numerous agents, including anagrelide, most importantly. However, the breadth of the patent does not in any way diminish its teachings. Stated another way, it is well understood in the art that the comprehensiveness of a disclosure does not negative its value for teaching each of the individual elements disclosed.

Applicant is assuming that, in the sentence "D'Angelo is a broad patent...," the D'Angelo reference should be replaced with the Miranda reference since Miranda, but not D'Angelo, discloses anagrelide. The Examiner continues by asserting that "the breath of the patent does not in any way diminish its teachings." If Applicant is construing the arguments of the Examiner correctly, it appears that the Examiner is arguing that even though anagrelide is mentioned only once in a laundry list of drugs to treat thrombosis in Miranda, the reference still discloses the use of anagrelide to treat thrombosis.

Applicant would like to reiterate that thrombosis and thrombocythemia are distinct conditions. Thrombosis is the formation of blood clots whereas thrombocythemia is a disorder associated with the increased or abnormal production of blood platelets. Although blood clotting can result from platelet aggregation, patients with thrombosis do not necessarily have thrombocythemia and patients suffering from thrombocythemia do not necessarily have thrombosis. Furthermore, not all antithrombotic drugs can be used to treat thrombocythemia. For example, Miranda lists argatroban and defibrotide as antithrombotic drugs in addition to anagrelide (*see* column 25, lines 56-59). Argatroban directly inhibits thrombin and defibrotide inhibits platelet aggregation. Neither of these drugs can treat thrombocythemia because neither drug reduces platelet production. Thus, the use of anagrelide to treat thrombocythemia is not disclosed or suggested in Miranda.

To summarize the argument related to the cited references made in the previous amendment and above,

(1) Lang discloses the use of anagrelide to treat thrombocythemia, but does not disclose or suggest any routes of administration for anagrelide.

(2) Miranda discloses a transdermal drug delivery system, but does not disclose or suggest the use of anagrelide to treat thrombocythemia.

(3) D'Angelo discloses a transdermal drug delivery system, but does not describe or suggest the administration of anagrelide and does not describe or suggest the treatment or prevention of thrombocythemia.

(4) Ferrini describes the topical administration, including the transdermal administration, of methanediphosphonic acid derivatives. Ferrini does not describe or suggest anagrelide or the treatment of thrombocythemia.

(5) Yarrington primarily teaches the treatment of thrombocytosis by administering 5-(4-chlorophenyl)-2,4-dimethyl-3H-1,2,4-triazole-3-thione. Yarrington discloses that this compound can be administered orally or parentally including by implant or injection. Anagrelide is briefly discussed in the background of the invention as a compound used to treat thrombocytosis (*i.e.*, thrombocythemia) without any discussion or suggestion of the mode of its administration.

Thus, the cited references taken either separately or in combination do not describe or suggest the treatment of thrombocythemia in patients afflicted by that disease by transdermally administering an effective amount of a skin permeable form of anagrelide to minimize first pass liver metabolism, 3-hydroxy anagrelide formation, and adverse cardiovascular side effects as recited in the amended claims.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered, that the amendment be entered, and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: March 28, 2008

Respectfully submitted,

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